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# Practical Computer-Assisted Dosing for Aminoglycoside Antibiotics

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**In principle, computer-assisted individualization of antibiotic dosing offers the prospect of better patient outcomes through improved dosing precision. In practice, however, the expertise in pharmacokinetics required to operate these programs has precluded their use by most physicians and pharmacists. We developed a computer program for individualization of dosing of aminoglycoside antibiotics under conditions in which access to experts in pharmacokinetics is impractical. The program is accurate, yet it requires less effort for data collection than previous drug dosing programs did. The program generates advice on a broad spectrum of topics, including dose adjustment, interpretation of measured drug concentrations in blood, and recommendations for monitoring drug concentrations. We tested its performance by prospectively comparing it with a clinical pharmacokinetic consultation service in a series of 78 consecutive patients. There were no differences in accuracy or bias in the prediction of drug concentrations. The rate of agreement between the program's dosing recommendations and those of the consultation service was 67 percent. This rate of agreement is typical of interexpert variation. In a stratified set of 24 of the 41 instances with significant disagreement regarding the recommended dose, experts ranked the program's recommendations as highly as those of the consultation service (95% confidence interval for difference in rank, $-0.30 < \chi < 0.47$). The results suggest that expert systems can be coupled with pharmacokinetic dosing programs to deliver high-quality clinical recommendations for administration of antimicrobial agents.**

Computer-assisted drug dosing has offered the promise of making quantitative decisions regarding drug therapy easier through improvement in the precision of drug dosing. This promise has not yet been realized, despite initial descriptions of such programs in the early 1970s. Bayesian forecasting, the standard approach for mathematical modeling to individualize drug dosing, was first described for digoxin in 1972 and 1973 by Sheiner and colleagues (20, 26). An alternative approach based on expert system methods was published by Gorry et al. (11) in 1978. The Bayesian approach to drug dose individualization has been applied to many drugs (7, 8, 15, 16, 19, 22, 23, 31), including aminoglycoside antibiotics and vancomycin.

Aminoglycoside antibiotics are an excellent example of a class of drugs for which computer-assisted dosing has been shown to be valuable. Numerous studies have documented a high prevalence of underdosing of aminoglycosides by physicians. Published reports suggest that therapeutic peak drug concentrations in blood are achieved in only 25 to 60% of patients (1–4, 10, 12, 29, 30). The abilities of physicians to adjust the doses after reviewing measured drug concentrations are poor. Anderson et al. (1) and Arroyo et al. (2) found that physicians inappropriately failed to take action in at least 40% of the situations in which the measured drug concentrations mandated a change in dosing. Access to advice from a pharmacokinetic consultation service (PCS) corrects problems with physician dosing decision making. In four randomized trials, dose adjustment by PCSs by Bayesian forecasting resulted in improvement in the rates of achieving therapeutic drug concentrations from 30 to 40% to over 90% (6, 9, 10, 12). Individualization of dosing has also been shown to improve patient outcomes. Two observational studies found decreased infection-related mortality rates after patients were treated with individualized doses of aminoglycosides (30, 33). Two randomized trials of intervention by a PCS that used Bayesian forecasting programs have been performed (6, 9). Both trials found an average reduction in the length of stay in the hospital of approximately 4 to 5 days when the dose was adjusted by a PCS. Both trials also found that clinical variables responded more quickly, arguing that improved drug efficacy is a way of reducing the length of stay in the hospital. Destache et al. (9) found a significant reduction in the febrile period in their trial. Burton et al. (6) found a higher response rate of infection, as defined by the multifactorial infection response criteria of Smith et al. (28).

For most hospitals and physicians, realization of the potential benefits of computer-assisted dosing may be difficult. The successes described above were not achieved by the computer programs themselves but by teams of clinicians who used the computer programs to supplement their knowledge of pharmacology and pharmacokinetics. The teams worked with the patients' physicians to interpret clinical data for each patient and to set concentration goals. The teams then used Bayesian forecasting programs (or other methods [33]) to determine what doses to use to achieve their concentration goals.

Provision of access to existing Bayesian forecasting programs would probably not lead to the better gains described above. The effort required to collect data for pharmacokinetic modeling in current programs is formidable. Considerable expertise is required to interpret the results of Bayesian regression analysis and to identify errors in the recorded data or potential changes in the pharmacokinetics of drugs in patients. Expertise is also required to choose target drug concentrations based on an appropriate balance of risk and benefit and to formulate therapeutic monitoring strategies. In

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the majority of medical institutions, experts are not available to help with these tasks. For a computer program to be a useful tool under such circumstances, it would have to be designed for use by nonspecialists. The program would have to help nonspecialists consider clinical factors and set concentration goals for treatment. Because of the skill level of the user, the burden of ensuring the quality of the advice rests with the program (instead of with the user, as in current Bayesian forecasting programs). Nonetheless, it is important that the drug dosing program provide advice without excessive effort from the program users. For nonspecialists, management of drug therapy is only a small (albeit important) part of clinical care.

## MATERIALS AND METHODS

**Program design.** As part of our research to adapt the design of drug dosing programs for use by nonspecialists, we developed a computer program to assist nonspecialists with aminoglycoside antibiotic therapy. The program is called the Aminoglycoside Therapy Manager (ATM). The spectrum of advice of the program is similar to that of a clinical PCS. This includes analysis of the drug dosing and sampling history, dose adjustment advice, advice for future sampling of drug concentrations and other laboratory tests, and identification of early nephrotoxicity. To meet these goals, the ATM program has, in addition to an implementation of Bayesian forecasting methods, specific subroutines for analysis and editing of drug concentration data. The program also has an expert system module that allows incorporation of clinical data and the judgments of experts into the dosing recommendations.

The ATM program models aminoglycoside pharmacokinetics by using a one-compartment open model with the parameters drug clearance ($CL_{drug}$) and volume of distribution. In the program, $CL_{drug}$ is modeled as a fraction of estimated creatinine clearance ($CL_{CR}$), that is, $CL_{drug} = CL_{CR\ (calculated)} \cdot k$ + constant. The parameter $k$ is estimated for each individual. $CL_{CR}$ is estimated by the method of Jelliffe (13) for changing creatinine values in blood when creatinine concentrations are not stable or by the more standard formula, $CL_{CR\ (calculated)} = [(140 - \text{age}) \cdot \text{weight}]/(70 \cdot CR_{blood})$, where $CR_{blood}$ is the creatinine concentration in blood. Modeling of $CL_{drug}$ as a fraction of $CL_{CR}$ allows the ATM program to use data from periods when a patient has a markedly different renal function than that at the time of a consultation with the program.

Individual pharmacokinetic parameters for dose evaluation are estimated by using Bayesian regression (25) on observed drug concentrations. The Bayesian regression uses prior knowledge of the distribution of model parameter estimates in a large group or population of patients to constrain maximum-likelihood nonlinear regression estimates of pharmacokinetic model parameters for the individual patient. Conceptually, Bayesian forecasting yields a balance between the parameter estimates that fit the observed data and prior probability of observing those parameters in a large group of patients. To illustrate the approach, for the case in which model parameters in the population are independent and distributed multivariate normal, Bayesian estimation is performed by finding the model parameter estimates that minimize the following objective function:

$$\text{objective function} = \sum_{i=1}^{nl} \frac{(Y_i - \hat{Y}_i)^2}{\phi} + \sum_{j=1}^{np} \frac{(\rho_j - \hat{\rho}_j)^2}{\sigma}$$

where $Y$ is the observed drug concentration, $\hat{Y}$ is the predicted drug concentration, $\phi$ is the standard deviation of the drug concentration measurement, $nl$ is the number of drug concentrations, $\rho$ is the model parameter estimate for the population, $\hat{\rho}$ is the model parameter estimate for the individual, $np$ is the number of model parameters, $\sigma$ is the standard deviation of parameter estimate for the population, $i$ is the index of each observed drug concentration, and $j$ is the index of each parameter in the pharmacokinetic model. The Bayesian objective function is a sum of the typical least-squares (or maximum likelihood) regression objective function (the first term) and a second term which weights parameter estimates by their prior likelihood in a large population. The inclusion of information about the prior distribution of parameter estimates in the population allows estimation of model parameters in an individual for whom least-squares regression methods would not be appropriate because of inadequate information (too few measured drug concentrations or drug concentrations measured at times inappropriate to yield adequate information about model parameters). In the ATM program, the search for the identification of the optimal model parameter estimates is performed by the Marquardt-Levenberg method (21).

The ATM program extends previous implementations of Bayesian forecasting by incorporating algorithms to automatically analyze and interpret drug concentration data prior to the inclusion of those data in the Bayesian estimation. The goal of this process is to identify and exclude erroneous or misleading data that occur because of drug concentration sampling problems or changes in the patient's physiology. The approach works in the following manner. For each observed drug concentration, the ATM program calculates a prediction and a standard deviation of the prediction (based on the covariance matrix) (21). When drug concentrations that precede the concentration under evaluation are available, the individual estimate of model parameters and the covariance matrix from the regression are used in the calculation. When no preceding drug concentration measurements are available, population estimates of model parameters and the population covariance matrix are used in the calculations. If there is less than a 10% chance of having observed the new drug concentration, given the prediction of the model and the standard deviation of prediction ($P$ value calculated by using a one-sided test and a normal distribution), then the drug concentration is labeled "unexpected."

If, in a series of drug concentrations being examined by the ATM program, there are no drug concentrations that occur after a concentration is identified as unexpected, ATM informs the user and advises the user to review the clinical circumstances surrounding drug sampling and consider obtaining a repeat drug concentration measurement. ATM further classifies unexpected drug concentrations by determining whether the concentration is likely to have occurred given the distribution of model parameters in the population. If the probability of observing the drug concentration on the basis of population model parameter estimates and the population covariance matrix is less than 10% ($P$ calculated by using a one-sided test and a normal distribution), the unexpected concentration is not used in the Bayesian regression. This is because it is unlikely that the unexpected drug concentration could have been observed in any patient, given the clinical circumstances.

If there are additional drug concentrations that follow an unexpected concentration in a time series, the ATM program attempts to classify the unexpected concentration as indicative of either an "error" or a "change" in pharmacokinet-

ics. The specific algorithms are described in detail in another report (17). Concentrations classified as error by the program are excluded from use in the Bayesian regression. If a change in pharmacokinetics is identified by the program, drug concentrations that occur prior to the change are excluded from Bayesian regression. By using the edited data, the ATM program then estimates the individual model parameters for the patient.

After data analysis, data editing, and Bayesian forecasting, the ATM program activates its expert system module to determine target peak and trough concentrations for the patient. The expert system works like a clinical algorithm. Clinical knowledge is represented by using the rules described previously (5). The rules known to the ATM program are kept in a file separate from the main program. Rules can be readily changed without altering the rest of the ATM program, so that the ATM program's clinical strategies can be adapted to reflect different clinical practices at different institutions.

In the expert system module, users are asked to enter clinical data to classify the patient's required intensity of therapy into one of five arbitrary levels. Clinical data that are used to classify the required intensity of therapy include whether the aminoglycoside is being given as primary coverage against gram-negative organisms (or in a synergistic combination), the suspected location of the infection, any antibiotic sensitivity data, and other data that are used as proxies for the severity of illness. Users then enter data to classify the risk of nephrotoxicity into one of three levels (low, moderate, or high). Classification of nephrotoxicity risk is based on a regression equation described by Sawyers et al. (24). Risk is modified accordingly when a patient is concurrently treated with other nephrotoxic drugs. Instead of estimating a risk of toxicity, the program can identify patients who have already experienced nephrotoxicity. A state of "probable nephrotoxicity" is identified when there has been either an observed decrease in renal function (from serum creatinine data) or an observed change in pharmacokinetic model parameters suggestive of reduced renal function when there has been more than 72 h of aminoglycoside therapy. The program informs the users when it identifies potential nephrotoxicity and advises the user to consider alternative antibiotic therapy.

Actual target peak and trough concentrations are chosen by combining the indices of the level of intensity of therapy and nephrotoxicity risk. The system then examines a broad range of possible drug doses and dosing intervals and calculates steady-state drug concentrations. Our experiences regarding how a consultation service works with physicians suggest to us that guidelines for therapy, rather than authoritarian prescriptions, are more effective tools of communication. In the spirit of a guideline, the ATM program displays up to three acceptable dosing regimens that come close to achieving target peak and trough concentration goals. A graph of the estimated steady-state peak and trough concentrations for each dose and the confidence intervals of prediction (±1 standard deviation) are displayed with the dosing recommendations. The ATM programs then displays patient-specific recommendations for future monitoring of drug concentrations and renal function based on the patient's severity of illness, the risk of nephrotoxicity, and the width of confidence intervals for peak and trough concentrations.

The ATM program runs on International Business Machines-compatible computers with 640 kilobytes of memory. Use of a computer equipped with a math coprocessor and VGA standard graphics is recommended. Below, we describe a study that tested the hypothesis that a drug dosing program, in the hands of a minimally skilled user, can generate advice with clinical quality equivalent to that of a PCS.

A prospective, single-blinded comparison of the quality of dosing advice provided by the ATM program with that provided by a PCS in consecutive patients was undertaken at the Palo Alto Veterans Affairs Medical Center between 1 September and 31 December 1989. All patients who were not undergoing hemodialysis and who had received either gentamicin or tobramycin and in whom at least one drug concentration was measured were enrolled in the study.

Patients were seen by the PCS while undergoing aminoglycoside treatment. The PCS carried out their consultations in a routine manner. The consultation included a trip to the bedside of each patient to research each patient's exact dosing and drug concentration sampling history. Drug administration and drug sampling were carried out in a manner routine for the hospital. Staff nurses administered drugs, and physician house officers drew blood samples for drug concentration determination (except in the intensive care units, where nurses performed this task). Blood samples for drug concentration determinations were obtained approximately 0.5 h after the end of aminoglycoside infusion for peak concentration determinations and shortly before the next dose for trough concentration determinations. There were no formal mechanisms to control the consistency of drug sampling times.

The PCS used DrugCalc (Metaphor Software, 1989), a commercial Bayesian forecasting program, to estimate individual pharmacokinetic parameters. DrugCalc has Bayesian estimation routines similar to those implemented in the ATM program, but it does not have the ability to model gentamicin clearance as a function of $CL_{CR}$ and does not have the ability to screen its data input to detect potential errors. Review of data quality and selection of the data to be included in the Bayesian forecast were integral parts of PCS review of a case. The PCS identified and reported a primary and two alternative dosing regimens that should produce appropriate drug concentrations in each patient. If only one or two regimens produced appropriate concentrations, then only those regimens were recommended by the PCS. The PCS did not have primary responsibility for dosing of patients. Instead, its goal was to assist the clinical pharmacists who monitored the patients on each hospital ward with the evaluation of the dose recommended by the physicians. Multiple dosing recommendations were generated by PCS to allow the pharmacists to judge whether currently ordered doses could be expected to produce results equivalent to those primarily recommended by PCS. If the ward pharmacist judged that the dose prescribed by the physician was unlikely to produce optimal results, the pharmacist contacted the physician and urged a dose adjustment by using PCS's recommendations.

To blind the consultation service to the program's recommendations during the trial, a special version of the ATM program in which only the data acquisition portions of the program were enabled was used to collect patient data. A pharmacy resident with no special training in pharmacokinetics or knowledge of the ATM algorithms collected patient data by using this program. Drug regimen orders were entered into the ATM program except when there were large discrepancies between the ordered and the administered drug regimens that should have been easily detected by a ward pharmacist or a physician (such as a missed dose or a

dose delivered hours late). Information on the timing and concentrations of drug in blood samples or other laboratory tests was obtained from the hospital information system. When the pharmacy resident had questions about the clinical meaning of individual data, she consulted another member of the study team, who was a board-certified internist.

After the period of data collection was completed, patient data were analyzed by using the full ATM program and the results were compared with those obtained by the PCS. An ATM consultation report was generated for each consultation performed by the PCS. If one of the ATM program's three recommendations was the same as a primary or either of the two secondary dosing recommendations of the PCS, we concluded that there was basic agreement between the recommendations. Cases without such an overlap were categorized as "disagreement in recommended dose."

Of the 41 of cases for which there was disagreement in the recommended dose, 24 cases were selected for closer study. These cases were selected to avoid repeat review of the same patient and to stratify the complexity of cases reviewed. Complexity was defined on the basis of the number of drug concentrations available and whether the ATM program had identified any unexpected drug concentrations. Four experts (Michael Winter, George Jaresko, Dennis Mungall, and Gary Matzke), all with significant experience in computer-based pharmacokinetic forecasting, in consultation with Roger Jelliffe, were recruited to help in the evaluation study. The experts were clinical pharmacists (except for Roger Jelliffe, a physician) who had considerable experience with clinical pharmacokinetic consultations. Each of the experts had published several peer-reviewed articles describing studies in which Bayesian forecasting methods were applied. Cases were distributed to experts in a round-robin fashion. Each expert gave a single dosing recommendation for six patients. In a second round of dosing recommendations for 18 patients, each expert reviewed and ranked the primary dosing recommendations of the program and the PCS and the dosing recommendation of one of the experts. Experts were blinded to the source of the recommendation. Reviewers also indicated whether each dosing recommendation was acceptable or unacceptable and specified their target peak concentration for each patient. Experts formulated recommendations and reviewed the cases by using their choice of Bayesian forecasting programs. All experts were compensated for their work. Statistical calculations were performed by using the StatView II program (Abacus Concepts, 1988).

## RESULTS

The PCS performed 128 consultations on 78 patients during the study period. The mean age of the patients was 62 ± 11 years (standard deviation) (age range, 92 to 19 years). Patients usually had normal or low initial creatinine concentrations in serum. The mean creatinine level in serum was 1.1 ± 0.8 μg/ml (standard deviation) (range, 0.3 to 7.9 μg/ml). The locations or types of infections treated and the number of patients with the infections were as follows: pneumonia, 17; cellulitis or osteomyelitis, 16; Pyelonephritis, 13; gastrointestinal tract, 10; Neutropenia with multiple possible sources, 8; other, 13. Approximately 70% of patients received aminoglycoside antibiotics as their primary coverage for gram-negative organisms.

The accuracy and bias of Bayesian predictions of future drug concentrations were not significantly different. There were 86 Bayesian predictions. Figures 1 and 2 show the mean accuracy and bias, respectively, for the Bayesian predictions of the ATM program and the consultation service. The 95% confidence interval for the difference in accuracy between the ATM program and the consultation service was $-0.18 < \chi < 0.14$ (two-sided, paired $t$ test).

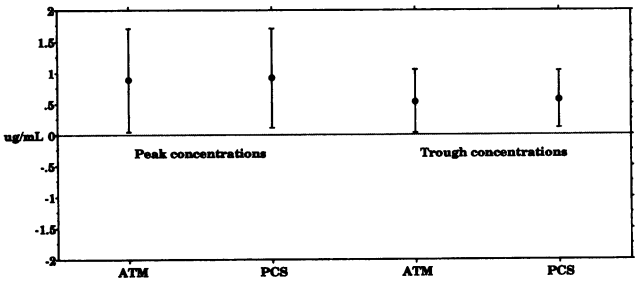


FIG. 1. Accuracy (mean absolute error) in prediction of peak and trough concentrations by the ATM program and the consultation service.

Overlap between one or more of the ATM program's three recommendations and one of the primary or secondary recommendations of the PCS occurred for 83 of the 124 (67%) dosing recommendations. For 30 of the 41 episodes categorized as disagreement in recommended dose, dosing recommendations were close; one of the PCS's recommendations was within 10 mg of one of ATM's recommended doses with the same dosing interval or the total daily doses were within 10% of each other.

The key clinical features of the cases (proportion of cases) submitted for review by the experts were as follows: concurrent administration of a broad-spectrum cephalosporin or extended-spectrum penicillin (50%), neutropenia (29%), cancer (33%), pneumonia (38%), and albumen level of <3.0 μg/ml (38%). Patients were, in general, severely ill. Half of the patients received concomitant therapy with a broad-spectrum cephalosporin, ticarcillin, or mezlocillin. Many patients were immunocompromised because of cancer, malnutrition, drug-induced neutropenia, or a combination of these factors.

In this group of patients, expert reviewers had no preference for the dosing recommendations of either the PCS or the ATM program. On a case-by-case basis, there was no difference in the mean rank given to dosing recommendations (95% confidence interval for the mean of the paired difference, $-0.30 < x < 0.47$; two-sided $t$ test). The results of analysis on a recommendation-by-recommendation basis were similar. Experts ranked the recommendations of the ATM program as high or higher that those of the PCS about 51% of the time (37 of 72 rankings). The rate that an

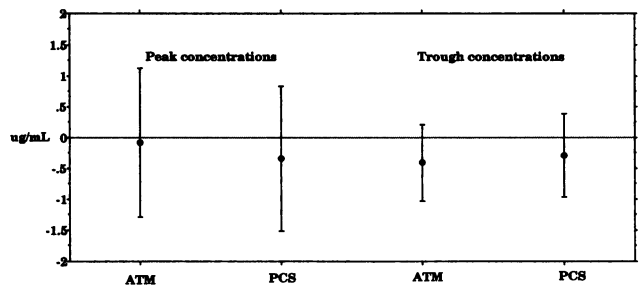


FIG. 2. Bias (mean error) in the prediction of peak and trough concentrations by the ATM program and the consultation service.

acceptable rating of a dose recommendation was obtained was similar for both groups. Experts rated 49 of 70 of the ATM program's and 46 of 70 of the PCS's recommendations as acceptable.

## DISCUSSION

One of the first medical expert systems developed was the MYCIN program, which recommended antibiotic therapy for patients with sepsis and meningitis (27). Several years later, a program called the Digitalis Therapy Advisor was developed by Gorry et al. (11). While that program focused on a different medical problem, it extended the design of the MYCIN program by combining a population pharmacokinetic model with an expert system. The population pharmacokinetic model was used to analyze the drug administration history to determine whether dosing had been adequate or potentially toxic to the patient. The expert system provided reasoning about the general actions that should be taken on the basis of the clinical scenario of drug administration, analysis of the dosing history, and evidence of response to the drug. The pharmacokinetic model was then reapplied to calculate specific dosing recommendations. The program performed well in a retrospective validation study, but it never came into routine clinical use. In the years since the development of the Digitalis Therapy Advisor program, Bayesian forecasting has become the standard for modeling of individual pharmacokinetics for dose adjustment. However, no current Bayesian drug dosing programs use integrated expert systems. The advantage of an integrated expert system, which has been well described by Gorry and coauthors (11), is that the expert system can capture the clinical expertise involved in dosing decisions.

The ATM program builds on the design of the Digitalis Therapy Advisor by adding Bayesian forecasting and the ability to automatically analyze data, identify potentially erroneous data, and alert the user to problems with the methodology of drug level measurement. Problems with the methodology of drug level measurement are common (18) and can lead to significant bias in the prediction of drug concentrations (14). The ATM program integrates its data analysis into expert system reasoning for dosing, becoming more conservative with unsure data or presumed changes in the patient's renal function. The ATM program also attempts to convey to users the uncertainty of predicting future drug concentrations and offers advice for therapeutic monitoring to reduce that uncertainty.

The ATM program, which uses "low-effort" data items such as drug dosing orders and approximate times of sampling of drug concentrations, was as accurate and as precise in the prediction of drug concentrations as the consultation service, which collected dosing histories in great detail. This is important, because nonspecialist users may have only limited amounts of time for data collection.

The overall rate of agreement of the dosing recommendations between the ATM program and the consultation service was 67 percent. This rate was similar to the rate of agreement seen among experts in infectious diseases in the validation study of MYCIN (32). In the sample of cases for which there were disagreements in the dosing recommendations, outside experts ranked the recommendations of the ATM program as highly as they did those of the PCS. The rate of unacceptable recommendations by the ATM program, while somewhat of a concern, was lower than that of the consultation service, suggesting that this is an area in which there are strong disagreements in the philosophy of drug therapy.

The expert system in the ATM program reflected the clinical knowledge and perceptions of risk and benefit of the developers of the program rather than those of the PCS or the outside experts. Improved rates of agreement (or fewer unacceptable ratings) could be achieved if the program's expert system was adapted to reflect the preferences of the PCS (or the outside experts). Because the ATM program has a modular expert system, this could be done by a programmer in several hours or even by another computer program on the basis of a questionnaire completed by a representative of the PCS.

Overall, the ATM program's performance, while not perfect, was as good as that of an established clinical PCS. Use of the ATM program may be an acceptable substitute for consultation with an expert in pharmacokinetics under circumstances in which such advice is not available. Further studies are needed to determine whether use of the ATM program will result in improvements in efficacy and cost reductions associated with dose adjustment by a PCS.

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